THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of the complete specification filed in respect of Patent application No.311/MAS/2002 dated 23rd April 2002 by Dr. Reddy's Laboratories Limited, an Indian Company having its registered office at 7-1-27, Ameerpet, Hyderabad – 500 016, Andra Pradesh, India .....

.....In witness thereof

I have hereunto set my hand

Dated this the 17th day of May2002
27th day of Vaisakha, 1924 (Saka)

(K.M. VISWANATHAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
CHENNAI – 600 018

FORM 2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

Novel Crystalline Polymorph Form-VI of Olanzapine and a Process for Preparation thereof

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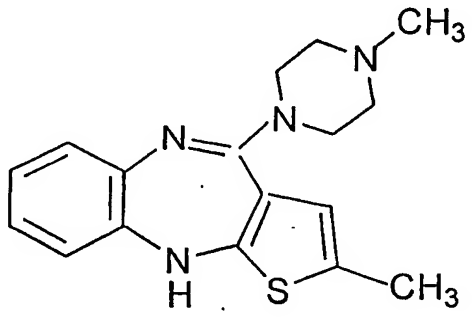
The following specification particularly describes the nature of this invention and the manner in which it is to be performed:

Field of Invention

The present invention relates to novel crystalline form of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and to a method of preparation there of. 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (Olanzapine) is represented by the following Structure.



Olanzapine is useful for treating psychotic patient and mild anxiety states. Preparation of Olanzapine and its acid addition salts, having pharmaceutical properties, particularly in the treatment of disorders of the central nervous system.

Background of Invention:

US 5,229,382 discloses the preparation of Olanzapine and its acid addition salts, having pharmaceutical properties, particularly in the treatment of disorders of the central nervous system and the patent does not refer to any specific polymorphic crystalline forms of Olanzapine.

EP 0 733 635 A1 claims Form-2 of Olanzapine. The patent also states that the product obtained according to the process described in US 5,229,382 as Olanzapine Form-1.

Furthermore, EP 0 733 635 A1 discloses the d values for Form-1 and Form-2 from their X-ray Diffractograms. The d values are as follows:

d value	d value
Form-1	**Form-2**
9.94	10.26
8.55	8.57
8.24	7.47
6.88	7.12
6.37	6.14
6.24	6.07
5.58	5.48
5.30	5.21
4.98	5.12
4.83	4.98
4.72	4.76
4.62	4.71
4.53	4.47
4.46	4.33
4.29	4.22
4.23	4.14
4.08	3.98
3.82	3.72
3.74	3.56

3.69	3.53
3.58	3.38
3.50	3.25
3.33	3.12
3.28	3.08
3.21	3.06
3.11	3.01
3.05	2.87
2.94	2.81
2.81	2.72
2.75	2.64
2.65	2.60
2.63	
2.59	

US 6,348,458 B1 discloses the preparation of a series of crystalline polymorphic forms of Olanzapine namely Form-III, Form-IV and Form-V. The d values for these forms from their X-Ray Diffractograms are also incorporated in the patent and are mentioned in the following Table-1.

Table-1:

Form-III	Form-IV	Form-V
d value	d value	d value
10.7476	9.9487	10.5932
10.3156	8.5074	10.2170
8.6245	8.2103	9.9503
7.1713	6.8673	8.5259
6.5014	4.9734	7.1016
6.1120	4.8172	6.0731
5.9251	4.7114	5.2041
5.8243	4.6122	4.9856
5.5165	4.5282	4.8153
5.2359	4.2340	4.7514
4.8541	4.0901	4.6139
4.7514	3.7574	4.5302
4.5578	3.6989	4.4714
4.4938	3.5052	4.2271
4.4536		4.1307
4.2588		4.0736
4.1523		3.9880
4.0699		3.7763
3.9898		3.7167
3.8955		3.5315
3.7288		3.3762
3.5626		3.0060
3.0262		

The novel crystalline polymorphic form of Olanzapine of the present invention is well distinguished from the crystalline polymorphic forms reported in the prior art and conveniently herein after, designated as Polymorph Form-VI of Olanzapine.

Hence present invention provides a novel crystalline polymorph Form-VI of Olanzapine and the present invention also embodies the process for the preparation of crystalline polymorph Form-VI of Olanzapine, more specifically the present invention is related to conversion of Polymorph Form-I of Olanzapine to novel crystalline polymorph Form-VI of Olanzapine.

Summary of the Invention

The present invention provides a novel crystalline polymorphic Form of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine (Olanzapine), conveniently designated as Polymorph Form-VI of Olanzapine. The invention also relates to provide the process for the preparation of crystalline polymorph Form-VI of Olanzapine, which comprises the stirring of polymorph Form-I of Olanzapine in alcoholic solvents to result the novel crystalline polymorph Form-VI of Olanzapine. The process of the present invention is eco friendly and well suited for industrial scale up.

Brief description of accompanying drawings:

Fig. 1 is an X-ray powder diffractogram of the substance obtained in the present invention.

Fig. 2 is a DSC thermogram of the substance obtained in the present invention.

Fig. 3 is an infrared absorption spectrum of the substance obtained in the present invention.

Detailed Description of the Invention:

Accordingly, the present invention provides novel crystalline polymorph Form-VI of Olanzapine and a process for the preparation there of.

The Crystalline nature of polymorph Form-VI of Olanzapine can be characterized by its X-ray diffractogram, Infrared spectrum and Differential scanning calorimetry thermogram.

The X-ray powder diffraction pattern of crystalline polymorph Form-VI of Olanzapine was measured on a Rigaku D/Max 2200 Powder Diffractometer with Cu Radiation source. The Crystalline polymorph Form-VI of Olanzapine has X-ray powder diffraction pattern essentially as shown in the Table-2. The X-ray powder diffraction pattern is expressed in the terms of its d values, and percentage intensity (in %).

Table-2:

d-values	Intensity (%)
10.2972	35
8.5646	6
7.6618	22
7.4935	21
7.3691	21
6.6317	25
6.5246	29
6.2320	87
5.7713	7
5.7121	9
5.3042	20
5.2174	6
4.9733	34
4.8335	7
4.7614	5
4.7162	8
4.6284	27
4.4802	13
4.3795	54
4.3163	77
4.2874	100
4.2308	21
4.1297	34
4.0958	34
4.0117	17
3.8275	24
3.7263	13
3.6509	17
3.5311	6

3.3141	29
3.2782	18
3.1207	17
3.0035	5
2.8824	5
2.8099	8
2.8014	6
2.0562	6

The present invention of crystalline polymorph Form-VI of Olanzapine is characterized by its X-ray powder diffraction as depicted in Figure (1).

The present invention also provides Differential Scanning Calorimetry thermogram of crystalline polymorph Form-VI of Olanzapine. The Differential Scanning Calorimetry thermogram exhibits a significant endo peak around 196 ^{o}C and as depicted in Figure (2).

The present invention further provides the Infrared data for crystalline polymorph Form-VI of Olanzapine, which was measured by KBr-transmission method with identified significant peaks around 3217 cm^{-1}, 2933 cm^{-1}, 1592 cm^{-1}, 1561 cm^{-1}, 1468 cm^{-1}, 1369 cm^{-1}, 1218 cm^{-1}, 1143 cm^{-1}, 1007 cm^{-1}, 964 cm^{-1}, 751 cm^{-1} and 674 cm^{-1}.

The present invention provides the IR spectrum of crystalline polymorph Form-VI of Olanzapine as depicted in Figure (3).

Accordingly, the present invention provides novel crystalline polymorphic Form-VI of 2-methyl-4- (4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine (Olanzapine), which comprises;

i) stirring polymorph Form-I of Olanzapine in alcoholic solvents such as n-butanol or tert.butanol, preferably n-butanol at a temperature of 0 to 40°C for 30 minutes to 10 hours;

ii) isolating the obtained solid form step (i) by conventional methods;

iii) drying the compound of step (ii) at a temperature of 40 to 100°C to afford the desired crystalline polymorph Form-VI of Olanzapine.

The present invention therefore provides novel Olanzapine Form-VI and a simple method for its preparation.

It is noteworthy to mention that the polymorph Form-I of Olanzapine was prepared as per the procedure disclosed in our co-pending Indian Patent application No. 709/MAS/2000.

Detailed description of accompanying drawings:

Fig. 1 is a characteristic X-ray powder diffraction pattern of novel crystalline polymorph Form-VI of Olanzapine.

(Vertical axis: Intensity (CPS); Horizontal axis: 2θ(degrees).

The significant d values obtained are 10.2972, 8.5646, 7.6618, 7.4935, 7.3691, 6.6317, 6.5246, 6.2320, 5.7713, 5.7121, 5.3042, 5.2174, 4.9733, 4.8335, 4.7614, 4.7162, 4.6284, 4.4802, 4.3795, 4.3163, 4.2874, 4.2308, 4.1297, 4.0958, 4.0117, 3.8275, 3.7263, 3.6509, 3.5311, 3.3141, 3.2782, 3.1207, 3.0035, 2.8824, 2.8099, 2.8014 and 2.0562 A°.

Fig. 2 is a characteristic Differential Scanning Calorimetric thermogram of novel crystalline polymorph of Form-VI of Olanzapine.

Vertical axis: Temperature (in ° C); Horizontal axis: Signal (in mV).

The Differential Scanning Calorimetric Thermogram exhibits a significant endo peak at 196 ° C.

Fig. 3 is a characteristic infrared absorption spectrum in potassium bromide of Olanzapine Form-VI.

[Vertical axis, Transmission (%); Horizontal axis: Wave number (cm^{-1})].

The characteristic peaks for Olanzapine Form-VI are indicated around 3217 cm^{-1}, 2933 cm^{-1}, 1592 cm^{-1}, 1561 cm^{-1}, 1468 cm^{-1}, 1369 cm^{-1}, 1218 cm^{-1}, 1143 cm^{-1}, 1007 cm^{-1}, 964 cm^{-1}, 751 cm^{-1} and 674 cm^{-1}.

Examples:

The present invention is described in detail with example given below that are provided by way of illustration only and therefore, should not be construed to limit the scope of the invention.

Preparation of Crystalline Polymorph Form-VI of Olanzapine:

Example 1

A mixture of polymorph Form- I of Olanzapine (10.0 g) and n-butanol (30 ml) was stirred at a temperature of 25 – 30°C for 1-2 hours. Further the compound was filtered, washed with n-butanol (5.0 ml) and dried at a temperature of 60 - 70 °C to a constant weight to render the desired crystalline polymorph Form-VI of Olanzapine. (Yield: 7.1grams, 71.0%).

We Claim:

1. A novel crystalline polymorph Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)- 10H-thieno[2,3-b][1,5] benzodiazepine (Olanzapine).
2. The crystalline polymorph Form-VI of Olanzapine of claim 1 having X-ray powder diffraction pattern with characteristic d-values (in A^{O}) and Intensity percentage (in %) as shown in the following table.

d-values	Intensity (%)
10.2972	35
8.5646	6
7.6618	22
7.4935	21
7.3691	21
6.6317	25
6.5246	29
6.2320	87
5.7713	7
5.7121	9
5.3042	20
5.2174	6
4.9733	34
4.8335	7
4.7614	5
4.7162	8
4.6284	27
4.4802	13
4.3795	54
4.3163	77
4.2874	100
4.2308	21
4.1297	34
4.0958	34
4.0117	17
3.8275	24
3.7263	13
3.6509	17
3.5311	6
3.3141	29
3.2782	18

3.1207	17
3.0035	5
2.8824	5
2.8099	8
2.8014	6
2.0562	6

3. The crystalline polymorph Form-VI of Olanzapine of claim 2 having an X-ray powder diffraction pattern as depicted in Figure (1).
4. The crystalline polymorph Form-VI of Olanzapine of claim 1 having differential scanning calorimetry thermogram which exhibits a characteristic endo peak around 196 ° C.
5. The crystalline polymorph Form-1 of Olanzapine of claim 4 having a differential scanning calorimetry thermogram as depicted in Figure (2).
6. The crystalline polymorph Form-VI of Olanzapine of claim 1 having identified characteristic peaks around 3217 cm^{-1}, 2933 cm^{-1}, 1592 cm^{-1}, 1561 cm^{-1}, 1468 cm^{-1}, 1369 cm^{-1}, 1218 cm^{-1}, 1143 cm^{-1}, 1007 cm^{-1}, 964 cm^{-1}, 751 cm^{-1} and 674 cm^{-1} in the Infra red Spectrum.
7. The crystalline polymorph Form-VI of Olanzapine of claim 6 having an Infrared spectrum as depicted in Figure (3).
8. A process for the preparation of novel crystalline polymorph Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (Olanzapine), which comprises;
   (i) stirring polymorph Form-I of Olanzapine in alcoholic solvents such as n-butanol or tert.butanol, preferably n-butanol at a temperature of 0 to 40°C for 30 minutes to 10 hours;

(ii) isolating the obtained solid form step (i) by conventional methods;

(iii) drying the compound of step (ii) at a temperature of 40 to 100°C to afford the desired crystalline polymorph Form-VI of Olanzapine.

9. The process as claimed in claim-8 of step (i), wherein the said alcohol is n-butanol.

10. A process as claimed in claim 1, for preparation of new crystalline polymorph Form-VI of Olanzapine, substantially as herein exemplified.

Dated this 18th day of April 2002.

(Signed) _____

Dr. R. Buchi Reddy,
Director (R&D),
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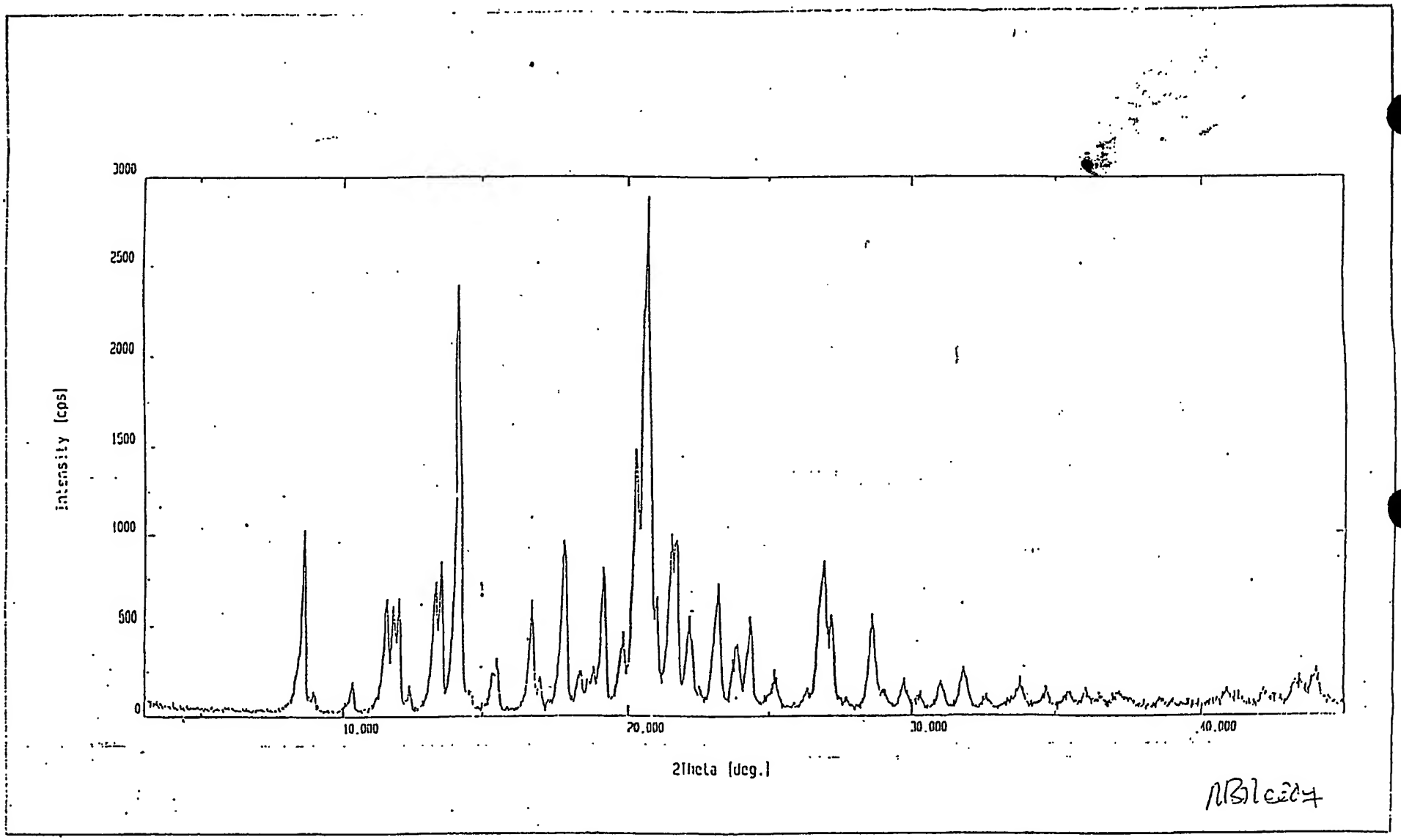

Fig. (1)

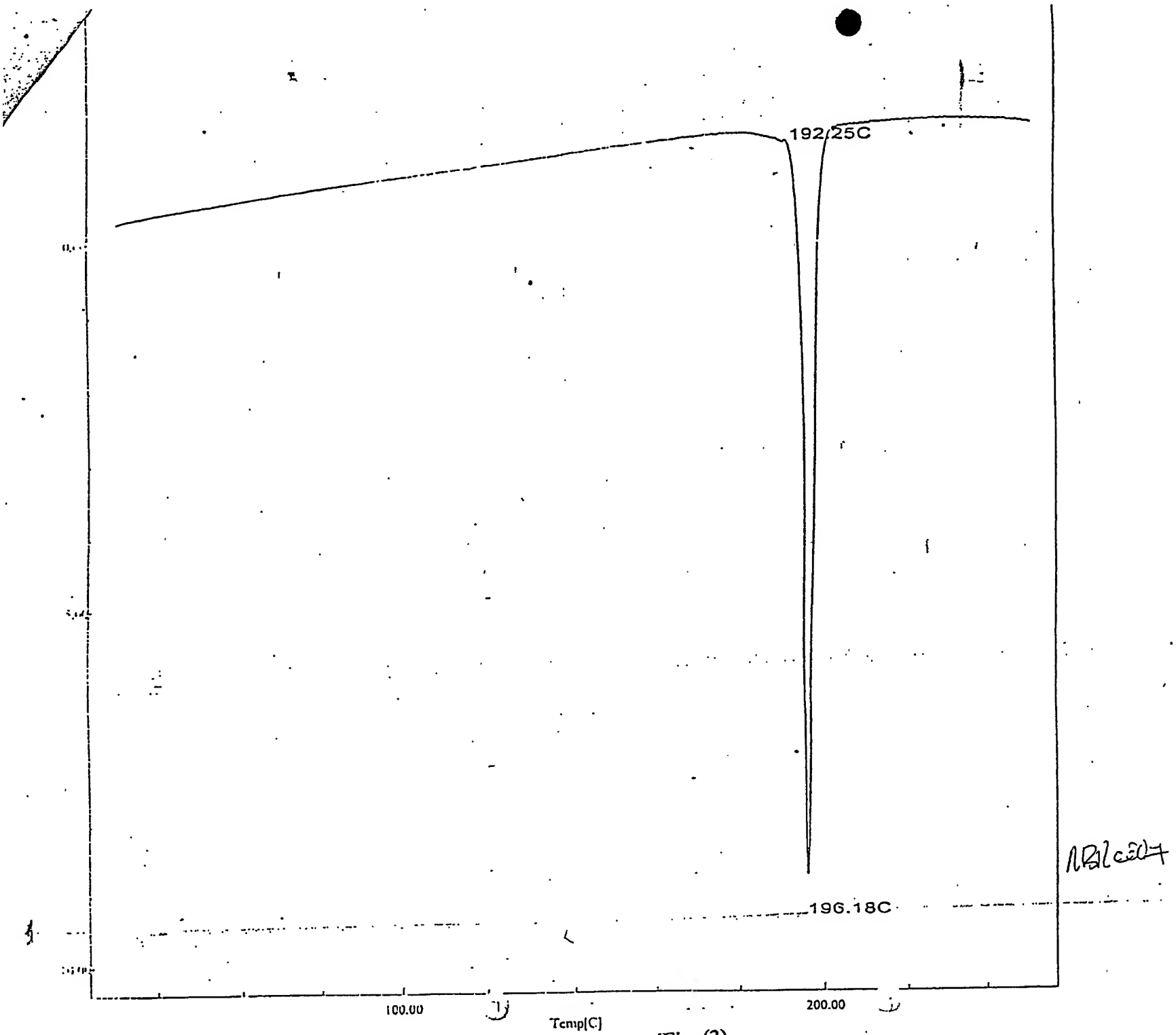

Fig. (2)

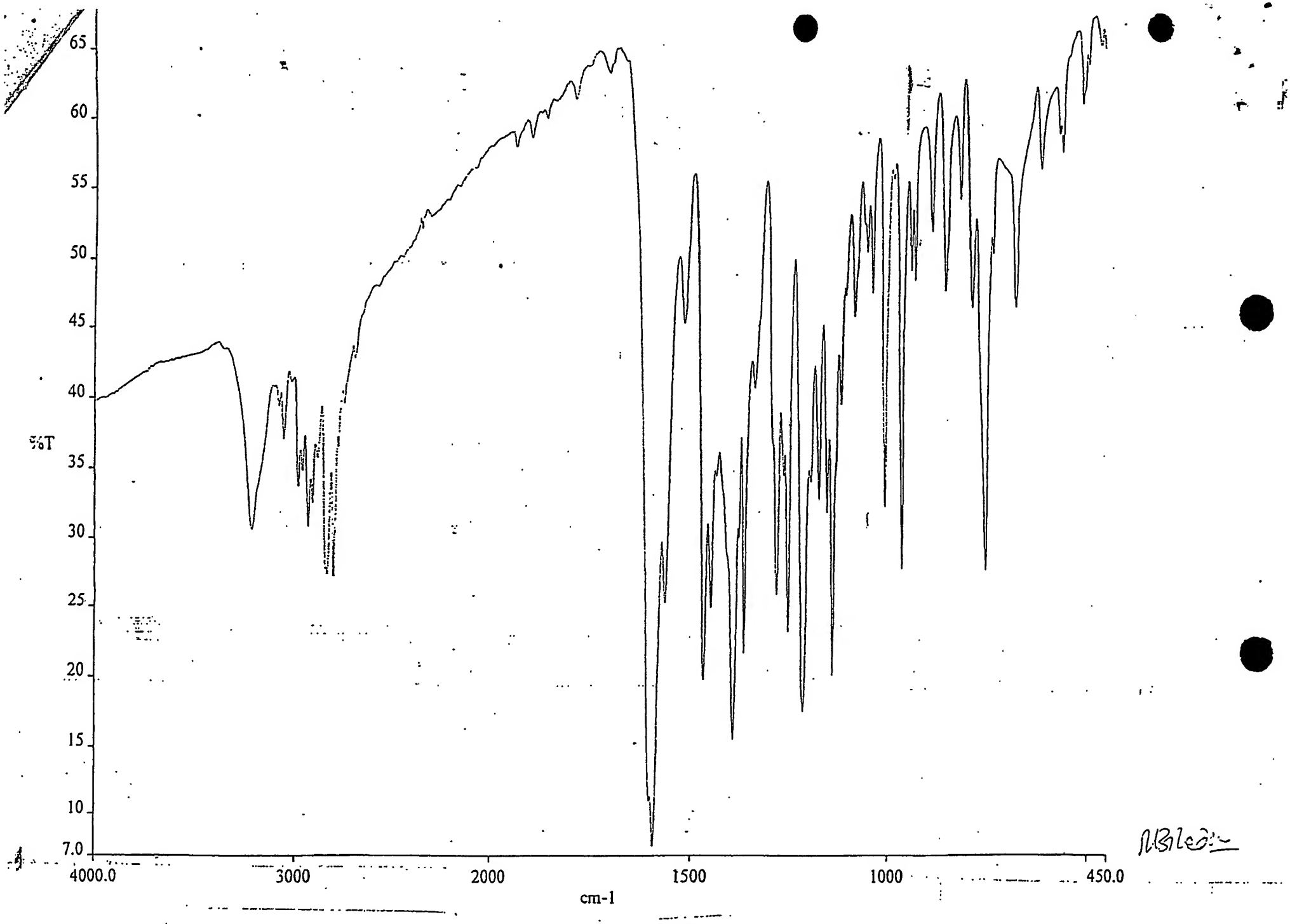
65
60
55
50
45
40
%T
35
30
25
20
15
10
7.0
4000.0
3000
2000
1500
1000
450.0
cm-1

Fig. (3)